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(54) Title: [11C]METHOXY-RADIOLABELLED 2,3',4,5'-TETRAMETHYLSTILBENE (TMS) AND ITS PREPARATION AND USE

(57) Abstract: This invention pertains generally to the field of radiochemical synthesis, and more specifically to methods of preparing [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) from an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) that has a pendant hydroxyl group, by reaction with [¹¹C]methyl trifluoromethanesulfonate (CF₃SO₂O¹¹CH₃), also known as [¹¹C]methyl triflate, or [¹¹C]methyl iodide (¹¹CH₃I). This reaction converts the pendant hydroxyl group into a pendant [¹¹C]methoxy group. The resulting [¹¹C]methoxy-radiolabelled product is useful, for example, as an in vivo positron emission tomography (PET) tracer, for example, for tumours (e.g., cancer tumours) and/or beta amyloid plaques (e.g., Alzheimer's disease). The present invention also pertains to the resulting [¹¹C]methoxy radiolabelled products, compositions comprising them, their use in methods of (e.g., PET) imaging, their use in methods of medical treatment and diagnosis, etc.

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**[11C]METHOXY-RADIOLABELLED
2,3',4,5'-TETRAMETHYLSTILBENE (TMS) AND ITS PREPARATION AND USE**

RELATED APPLICATION

This application is related to United States provisional patent application number 60/945,625 filed 22 June 2007, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

This invention pertains generally to the field of radiochemical synthesis, and more specifically to methods of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound from an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) that has a pendant hydroxyl group, by reaction with [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$), also known as [^{11}C]methyl triflate, or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$). This reaction converts the pendant hydroxyl group into a pendant [^{11}C]methoxy group. The resulting [^{11}C]methoxy-radiolabelled product is useful, for example, as an in vivo positron emission tomography (PET) tracer, for example, for tumours (e.g., cancer tumours) and/or beta amyloid plaques (e.g., Alzheimer's disease). The present invention also pertains to the resulting [^{11}C]methoxy-radiolabelled products, compositions comprising them, their use in methods of (e.g., PET) imaging, their use in methods of medical treatment and diagnosis, etc.

BACKGROUND

Throughout this specification, including any claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps, but not the exclusion of any other integer or step or group of integers or steps.

It must be noted that, as used in the specification and any appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

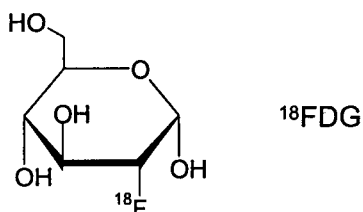
Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values

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are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

The key to long term survival for cancer patients is early detection and Positron Emission Tomography (PET) is the most sensitive technique for early detection of cancers. FDG-PET ($[^{18}\text{F}]$ -deoxyglucose) is invaluable in the imaging of a number of tumour types; however, it is not suitable for detection of all tumours. The reasons for this include: high uptake of FDG by normal tissues; inability to differentiate some low/medium grade tumours from benign lesions; limited use in the diagnosis of some recurrent tumours; and accumulation of FDG in inflammation making it indistinguishable from tumour tissue. Other PET tracers, with greater tumour specificity, are therefore required.



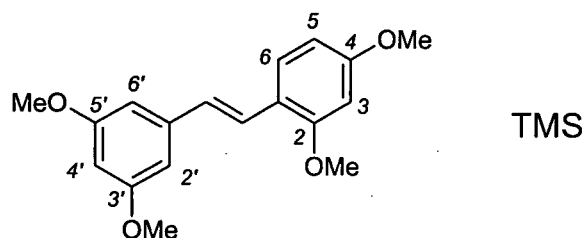
Malignant tumour cells can abnormally express or over-express proteins which are consequently potential targets for imaging with radiolabelled substrate analogues. In one approach inhibitors of such proteins are labelled. The inhibitor must be capable of being rapidly radiolabelled in order to be useful as a PET tracer, due to the short half-lives of the radiotracers (for ^{11}C , the half-life, $t_{1/2}$, is 20 minutes), and it must disassociate very slowly from the target. A number of enzymes, including monoamine oxidase (see, e.g., Fowler et al., 1987), cAMP-specific phosphodiesterase (see, e.g., DaSilva et al., 2002) and nitric oxide synthase (see, e.g., Zhang et al., 1996), have been successfully labelled with ^{11}C -inhibitors in imaging studies.

CYP1B1 is an enzyme from the Cytochrome P450 family of enzymes that is involved in the metabolic activation of several polycyclic aromatic hydrocarbon carcinogens. In many studies (see, e.g., Murray et al., 1997; Murray et al., 2001; Larsen et al., 1998; Eltom et al., 1998; Cheung et al., 1999), the presence of CYP1B1 has been shown to be specific to tumour tissue. Using immunohistochemistry, CYP1B1 was found to be absent from all 130 samples of normal human tissue from 16 different anatomical regions. In contrast, the CYP1B1 protein was present in 122 of 127 samples (96%) of malignancies from each of these 16 anatomical regions. The tumour-specific expression of CYP1B1 is being

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exploited via a cancer therapeutic designed to boost the immune system against tumour cells expressing CYP1B1.

5 A number of inhibitors of CYP1B1 have been developed, the most selective of which is 2,3',4,5'-tetramethoxystilbene (TMS). TMS inhibits CYP1B1 with high specificity (50-fold selectivity over CYP1A1 and 500-fold selectivity over CYP1A2 (these are the other two members of the CYP enzyme family) (see, e.g., Chun et al., 2001).



10 The inventors have recognized that because TMS is metabolized by CYP1B1 at a very slow rate, the molecule can be labelled at any position.

15 The inventors have also recognized that because TMS acts by interacting with (binding to) CYP1B1, and because CYP1B1 is specific to tumour cells, suitably labelled TMS could be used to image tumour cells, e.g., by using a method of PET imaging with suitably labelled TMS.

20 The inventors have also recognized that because TMS binds to beta amyloid plaques, suitably labelled TMS could be used to image beta amyloid plaques, e.g., by using a method of PET imaging with suitably labelled TMS.

25 The inventors have recognized that because TMS is metabolized very slowly, it can be labelled at any position, for example, at one or more of the pendant methoxy groups. (That is, there is no need to introduce the label to ring or backbone position.)

30 The inventors have applied labelling methods to TMS in order to prepare [¹¹C]methoxy-labelled TMS, which can be used both to image (e.g., PET image) tumours and beta amyloid plaques and to treat tumours diseases associated with beta amyloid plaques (e.g., Alzheimer's disease).

SUMMARY OF THE INVENTION

One aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

5

Another aspect of the present invention pertains to a pharmaceutical composition comprising a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

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Another aspect of the present invention pertains to a pharmaceutical composition comprising a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound which is *obtained by, or is obtainable by*, a method as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

15

Another aspect of the present invention pertains to a method of preparing a pharmaceutical composition comprising admixing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

20

Another aspect of the present invention pertains to a method of preparing a pharmaceutical composition comprising admixing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound which is *obtained by, or is obtainable by*, a method as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

25

Another aspect of the present invention pertains to method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

30

Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging that employs a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

35

Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging that employs a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or is obtainable by*, a method as described herein.

Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging, that includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

5

Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging, that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

10

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, for use in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

15

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or is obtainable by*, a method as described herein, for use in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

20

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

25

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or is obtainable by*, a method as described herein, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

30

Another aspect of the invention pertains to use of a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, as part of a method of imaging, for example, a method of positron emission tomography (PET).

35

Another aspect of the invention pertains to use of: (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, for use as a diagnostic or prognostic agent.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, for use as a diagnostic or prognostic agent.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to a method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body which includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

Another aspect of the present invention pertains to a method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

In one embodiment, the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour (e.g., a cancer tumour characterised by the expression or over-expression of CYP1, e.g., CYP1B1).

In one embodiment, the diagnosis or prognosis is diagnosis or prognosis of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease).

Another aspect of the present invention pertains to a method of treatment comprising administering an effective amount of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, to a patient in need of treatment.

Another aspect of the present invention pertains to a method of treatment of the human or animal body that comprises administering an effective amount of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, to a patient in need of treatment.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, for use in a method of treatment (e.g., of a disease condition) of the human or animal body by therapy.

Another aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, for use in a method of treatment (e.g., of a disease condition) of the human or animal body by therapy.

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.

Another aspect of the present invention pertains to use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein, which is *obtained by, or obtainable by*, a method described herein, in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.

Another aspect of the present invention pertains to use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.

Another aspect of the present invention pertains to a method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body which includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound, as described herein.

Another aspect of the present invention pertains to a method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

In one embodiment, the treatment is treatment of a cancer tumour (e.g., a cancer tumour characterised by the expression or over-expression of CYP1, e.g., CYP1B1).

In one embodiment, the treatment is treatment of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease).

Another aspect of the present invention pertains to novel intermediates, as described herein, which are suitable for use in the methods of synthesis described herein.

Another aspect of the present invention pertains to the use of such novel intermediates, as described herein, in the methods of synthesis described herein.

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspect of the invention.

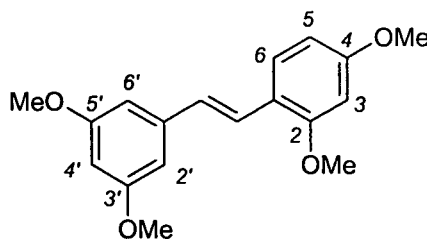
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows (top) the UV chromatogram (UV absorbance versus time) recorded for a solution of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) showing a retention time of 21.4 minutes; and (bottom) the radioactivity chromatogram (radioactivity versus time) recorded for the same solution (radiochemical purity 91%), also showing a retention time of 21.4 minutes. (The peaks at 18.7 and 29.9 minutes are unidentified.)

DETAILED DESCRIPTION OF THE INVENTION

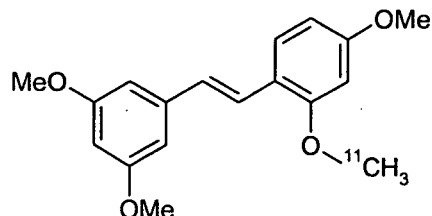
The present invention relates generally to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compounds, methods for their preparation, their use, etc.

The structure of 2,3',4,5'-tetramethoxystilbene (TMS) is shown below:

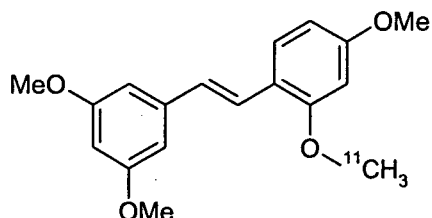


One aspect of the present invention pertains to a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound selected from [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) and pharmaceutically acceptable salts, solvates, and hydrates thereof.

In one preferred embodiment, the compound (e.g., the [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound), is selected from compounds of the following formula and pharmaceutically acceptable salts, solvates, and hydrates thereof:



In one preferred embodiment, the compound (e.g., the [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound) is:



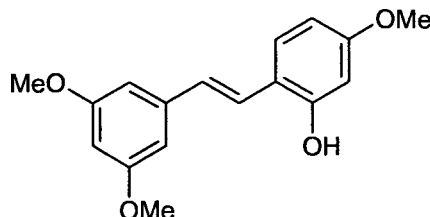
Methods of [^{11}C]Methoxy-Radiolabelling

One aspect of the present invention pertains to methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

In one embodiment, the method is a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) from an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) that has a pendant hydroxyl group, by reaction with [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$), also known as [^{11}C]methyl triflate, or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$). This reaction converts the pendant hydroxyl group into a pendant [^{11}C]methoxy group.

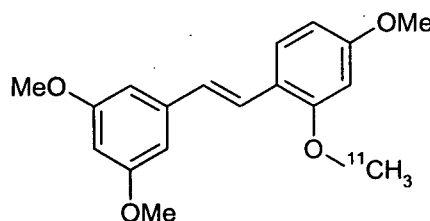
For the avoidance of doubt, the term "an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS)", as used herein, is intended to refer to a compound that is the same as 2,3',4,5'-tetramethoxystilbene (TMS) except that exactly one of the four methoxy groups (-OMe) is replaced with a hydroxyl group (-OH).

In one preferred embodiment, the unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) is a compound of the following formula:

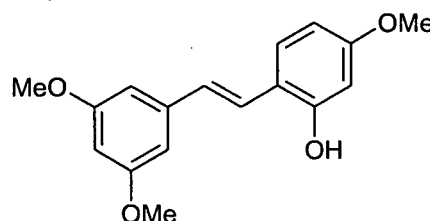


- 5 In one embodiment, the method is a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) comprising the step of reacting an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) that has a pendant hydroxyl group with [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$), also known as [^{11}C]methyl triflate, or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$) so as to convert said pendant hydroxyl group into a pendant [^{11}C]methoxy group.
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In one embodiment, the method is a method of a preparing a [^{11}C]methoxy-radiolabelled compound of the following formula:

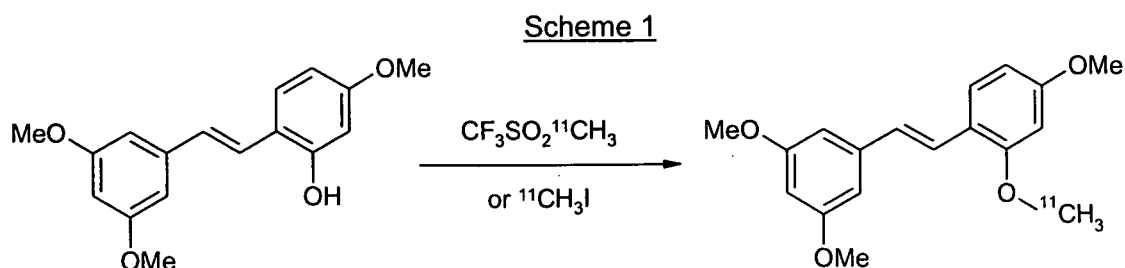


- 15 said method comprising the step of reacting a compound of the following formula:



with [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$) or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$) to give said [^{11}C]methoxy-radiolabelled compound.

- 20 An example of such an embodiment is illustrated in the following scheme.



The unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) may be prepared, for example, by using or adapting the methods described herein.

- 5 One aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) *obtained* by such a method.

One aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) *obtainable* by such a method.

10

Reagents, Reaction Conditions, and Purification

In one embodiment, the reaction is reaction with [^{11}C]methyl triflate.

- 15 In one embodiment, the reaction is reaction with [^{11}C]methyl iodide.

In one embodiment, the reaction is performed in the presence of a suitable Bronsted base. Examples of suitable Bronsted bases include, but are not limited to carbonates and bicarbonates, e.g., alkali metal carbonates and bicarbonate, e.g., sodium and potassium carbonates and bicarbonate, e.g., potassium carbonate (K_2CO_3).

20

In one embodiment, the reaction is carried out in aqueous media. For example, in one embodiment, the [^{11}C]methyl triflate is introduced into an aqueous solution (or suspension) of unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (optionally) a suitable Bronsted base, e.g., potassium carbonate (K_2CO_3), to form a reaction mixture.

25

In one embodiment, the reaction mixture (e.g., of [^{11}C]methyl triflate; unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS); and optionally Bronsted base) is mixed (e.g., stirred), e.g., for a mixing (e.g., stirring) time of about 1-30 minutes (e.g., about 1-10 minutes; e.g., about 5 minutes).

30

In one embodiment, the reaction is carried out at ambient or room temperature (e.g., 20°C-25°C).

35

In one embodiment, the reaction is carried out under an inert atmosphere (e.g., argon).

For example, an argon filled vial equipped with a magnetic stirring bar is filled with a solution of unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and K_2CO_3 in sterile water and subsequently placed on a magnetic stirrer 5 minutes prior to end of bombardment (EOB). [^{11}C]methyl triflate is then trapped in the solution. The

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trapped amount usually reaches a maximum after a number of minutes (from EOB). The magnetic stirrer is then switched on and the solution stirred for 5 minutes at room temperature (e.g., 20°C-25°C) resulting in the [¹¹C]methylation of the unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS).

In one embodiment, the resulting [¹¹C]-radiolabelled product is purified using ion exchange methods, e.g., with ion exchange media, e.g., using cation exchange methods, e.g., with cation exchange media, e.g., a cation exchange cartridge, e.g., a small disposable cation exchange cartridge.

For example, the reaction mixture may be transferred to a cation exchange cartridge (immobilising the [¹¹C]-radiolabelled product), which is then washed, e.g., with ethanol and sterile water. Washing removes not only unreacted starting material but also up to 98% of the radioactive [¹¹C]by-products. The cartridge is then eluted, e.g., with sodium chloride solution, e.g., sterile 0.9% w/v sodium chloride solution, to release the [¹¹C]-radiolabelled product.

The synthesis (and optionally purification) may readily be performed very quickly, e.g., in less than 60 minutes, e.g., in less than 45 minutes, e.g., in less than 40 minutes, e.g., in less than 35 minutes, e.g., in 10-60 minutes, e.g., in 10-45 minutes, e.g., in 10-40 minutes, e.g., in 10-35 minutes, e.g., in 15-60 minutes, e.g., in 15-45 minutes, e.g., in 15-40 minutes, e.g., in 15-35 minutes, e.g., in 20-60 minutes, e.g., in 20-45 minutes, e.g., in 20-40 minutes, e.g., in 20-35 minutes; from the end of bombardment (EOB).

It is anticipated that synthesis yield and product purity can be further improved by optimisation, for example, optimisation of the bombard time and intensity, reaction solvents, reaction conditions (e.g., temperature), etc.

Radiochemical purity and specific activity of the [¹¹C]-radiolabelled product (solution) may be determined using, for example, HPLC.

The identity of the [¹¹C]-radiolabelled product may be confirmed, for example, by co-injection with the corresponding unlabelled product, and noting that the retention time is identical for both.

In one embodiment, the method provides a radiochemical purity greater than 90%, preferably greater than 95%, preferably greater than 96%, preferably greater than 97%.

In one embodiment, the method provides a radiochemical yield of at least 2%, preferably at least 3%, preferably at least 4%, e.g., 4-10%, e.g., 4-6%.

In one embodiment, the method provides a product with a specific average activity of at least 0.5 GBq/ μ mol, preferably at least 1.0 GBq/ μ mol, preferably at least 1.5 GBq/ μ mol.

Preparation of Radiolabelled Methylating Reagents

In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, employ the methylating reagent [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{S}(=\text{O})_2\text{O}-^{11}\text{CH}_3$), also known as [^{11}C]methyl triflate, or the methylating reagent [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$).

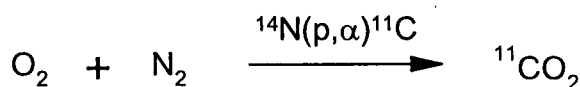
[^{11}C]methyl iodide is not only the fastest reacting methyl halide in nucleophilic substitution ($\text{S}_{\text{N}}2$) reactions such as N-, O- and S-methylation procedures (see, e.g., Bolton, 2001), but it is also regarded as the most commonly used labelling agent for the preparation of ^{11}C -radiotracers (see, e.g., Nagren et al., 1995).

[^{11}C]Methyl triflate has been used in radioactive labelling reactions (see, e.g., Bolton, 2001; Jewett, 1992; Iwata et al., 2001; Nagren et al., 1995; Lundkvist et al., 1998; Nagren et al., 1998). None of these publications teach or suggest the use of [^{11}C]methyl triflate in the methods described herein.

[^{11}C]Methyl iodide and [^{11}C]methyl triflate may be prepared, for example, using the methods discussed below.

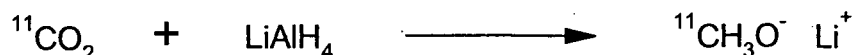
In a first step ("irradiation"), a mixture of nitrogen and oxygen, at high pressure (e.g., about 1-5 MPa, e.g., about 2 MPa) is subjected to bombardment with high energy (e.g., about 5-20 MeV, e.g., about 10 MeV) protons to form $^{11}\text{CO}_2$ via a $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ nuclear reaction. A beam current of about 10-100 μA (e.g., about 30 μA) and an irradiation time of about 1-120 minutes (e.g., about 10 minutes) is suitable.

Scheme 2

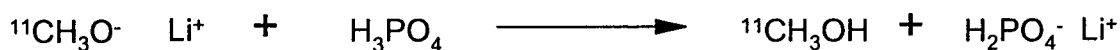


In a second step ("methoxide formation"), the resulting $^{11}\text{CO}_2$ is reduced to form $^{11}\text{CH}_3\text{O}^-$, using a suitable reducing agent, for example, lithium aluminium hydride (LiAlH_4 , LAH). See, for example, Crouzel et al., 1987. At the "end of bombardment2 (EOB)", $^{11}\text{CO}_2$ is transferred, for example, in a stream of helium gas, into a solution of LAH, for example, a cooled 0.1 M solution of LAH in tetrahydrofuran (THF). The $^{11}\text{CO}_2$ reacts with LAH to produce the $^{11}\text{CH}_3\text{O}^-$. The solvent (e.g., THF) may be removed by heating, for example, to 130°C.

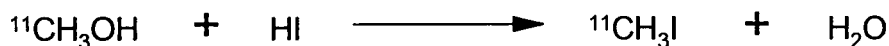
- 15 -

Scheme 3

In a third step ("neutralisation"), the resulting $^{11}\text{CH}_3\text{O}^-$ is neutralised to form the corresponding alcohol, $^{11}\text{CH}_3\text{OH}$, using, for example, a Bronsted acid, for example, phosphoric acid. For example, after removal of solvent, the $^{11}\text{CH}_3\text{O}^-$ is cooled, for example, to 0°C, phosphoric acid (e.g., 1 ml of 10% phosphoric acid) is added.

Scheme 4

In a fourth step ("iodination"), the resulting $^{11}\text{CH}_3\text{OH}$ is then reacted with hydroiodic acid (HI). For example, the $^{11}\text{CH}_3\text{OH}$ is transferred, e.g., distilled, to another reaction containing HI, and, for example, heated, for example, to 100-150°C (e.g., 135°C) to produce $^{11}\text{CH}_3\text{I}$.

Scheme 5

This [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$) may be used in the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

In a fifth step ("triflate formation"), the resulting $^{11}\text{CH}_3\text{I}$ is then reacted with a suitable triflate salt, for example silver triflate (AgCF_3SO_3). The reaction may conveniently be performed using column methods, for example, using a column packed with silver triflate. See, for example, Jewett, 1992. For example, a suitable column (e.g., stainless steel HPLC C-18 Luna column (250 x 3 mm)) is loosely packed with coarse silver triflate, and held in place with, for example, glass wool. Before use, the column is suitably conditioned, for example, under argon gas flow for 30 minutes at 300°C. The $^{11}\text{CH}_3\text{I}$, in a stream of carrier gas, for example, helium gas, is then passed through the column which is heated to a suitable temperature, for example, about 100-300°C (e.g., about 200°C), to yield the desired $\text{CF}_3\text{S}(=\text{O})_2\text{O}-^{11}\text{CH}_3$.

Scheme 6

This [^{11}C]methyl triflate ($\text{CF}_3\text{S}(=\text{O})_2\text{O}-^{11}\text{CH}_3$) may be used in the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

5 In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, employ the methylating reagent [^{11}C]methyl trifluoromethanesulfonate ($\text{CF}_3\text{S}(=\text{O})_2\text{O}-^{11}\text{CH}_3$), also known as [^{11}C]methyl triflate.

10 In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) further comprise the earlier step of (5) triflate formation.

In one embodiment, the methods further comprise the earlier steps of (4) iodination and (5) triflate formation.

15 In one embodiment, the methods further comprise the earlier steps of (3) neutralisation, (4) iodination, and (5) triflate formation.

In one embodiment, the methods further comprise the earlier steps of (2) methoxide formation, (3) neutralisation, (4) iodination, and (5) triflate formation.

20 In one embodiment, the methods further comprise the earlier steps of (1) irradiation, (2) methoxide formation, (3) neutralisation, (4) iodination, and (5) triflate formation.

25 In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, employ the methylating reagent [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$).

30 In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) further comprise the earlier step of (4) iodination and (5) triflate formation.

In one embodiment, the methods further comprise the earlier steps of (3) neutralisation and (4) iodination.

35 In one embodiment, the methods further comprise the earlier steps of (2) methoxide formation, (3) neutralisation, and (4) iodination.

In one embodiment, the methods further comprise the earlier steps of (1) irradiation, (2) methoxide formation, (3) neutralisation, and (4) iodination.

Preparation of Unlabelled Hydroxy Precursors of 2,3',4,5'-Tetramethoxystilbene (TMS)

The unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) may be prepared, for example, by using or adapting the methods described herein.

In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) further comprise the earlier step of (d) hydroxy deprotection.

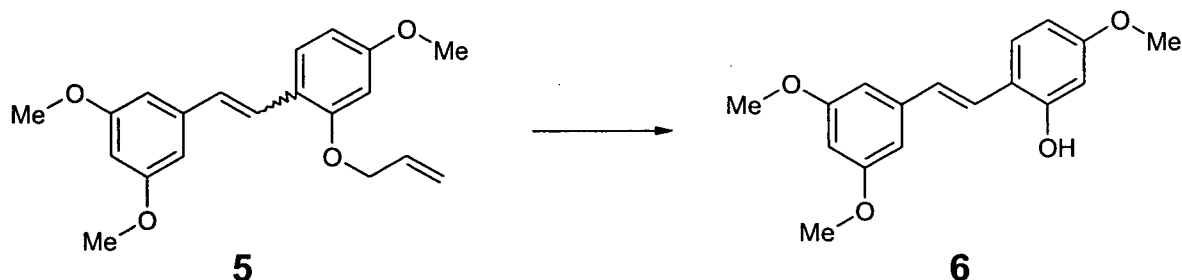
In one embodiment, the methods further comprise the earlier steps of (c) ring concatenation and (d) hydroxy deprotection.

In one embodiment, the methods further comprise the earlier steps of (b) hydroxy protection, (c) ring concatenation, and (d) hydroxy deprotection.

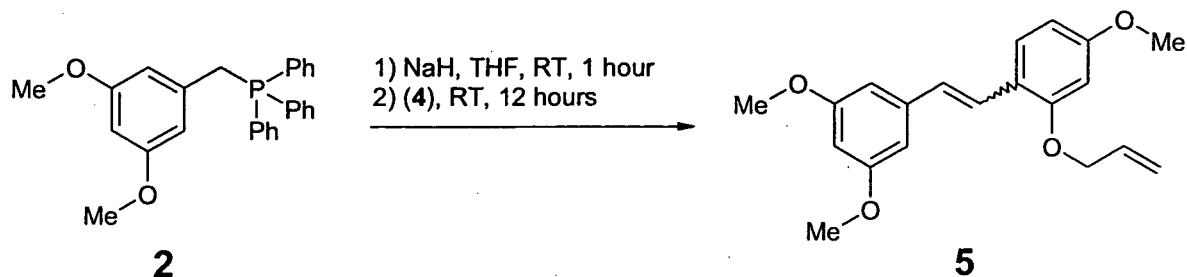
In one embodiment, the methods further comprise the earlier steps of (a) phosphine formation, (c) ring concatenation, and (d) hydroxy deprotection.

In one embodiment, the methods further comprise the earlier steps of (a) phosphine formation, (b) hydroxy protection, (c) ring concatenation, and (d) hydroxy deprotection.

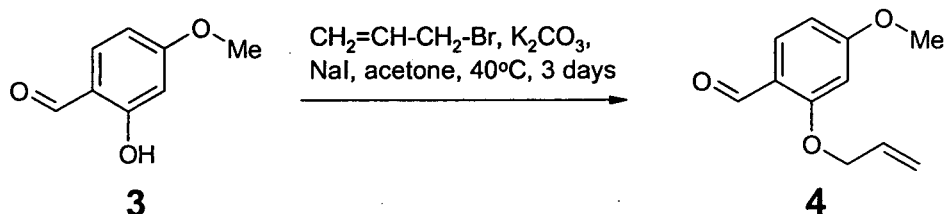
In one embodiment, the (d) hydroxy deprotection step is a step in which 2-(protected hydroxyl)-3',4,5'-trimethoxystilbene, for example, 2-allyloxy-3',4,5'-trimethoxystilbene (**5**), is deprotected to give 2-[(E)-2-(3,5-dimethoxy-phenyl)-vinyl]-5-methoxy-phenol (**6**), which is an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS). Such a step is illustrated in the following scheme.

Scheme 7

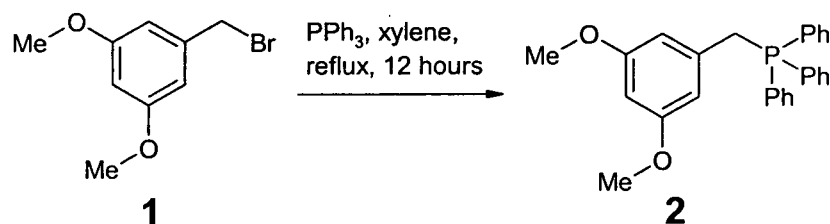
In one embodiment, the (c) ring concatenation step is a step in which (3,5-dimethoxy-benzyl)-triphenyl- λ^5 -phosphane (**2**) is reacted with a 2-(protected hydroxyl)-4-methoxy-benzaldehyde, for example, 2-allyloxy-4-methoxy-benzaldehyde (**4**), to give 2-(protected hydroxyl)-3',4,5'-trimethoxystilbene, for example, 2-allyloxy-3',4,5'-trimethoxystilbene (**5**). Such a step is illustrated in the following scheme.

Scheme 8

In one embodiment, the (b) hydroxy protection step is a step in which 2-hydroxy-4-methoxy-benzaldehyde (**3**) protected, for example, by reaction with a haloalkyl group, for example, 3-bromo-propene, to give a 2-(protected hydroxyl)-4-methoxy-benzaldehyde, for example, 2-allyloxy-4-methoxy-benzaldehyde (**4**). Such a step is illustrated in the following scheme.

Scheme 9

In one embodiment, the (a) phosphine formation step is a step in which 1-bromomethyl-3,5-dimethoxy-benzene (**1**) is reacted with triphenylphosphine to give (3,5-dimethoxybenzyl)-triphenyl- λ^5 -phosphane (**2**). Such a step is illustrated in the following scheme.

Scheme 10

Automation

In one embodiment, the methods of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) is partially or fully automated.

In one embodiment, the method is fully automated.

The method may be automated using well known apparatus and techniques.

Compositions

5 Another aspect of the present invention pertains to a pharmaceutical composition comprising [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

10 Another aspect of the present invention pertains to a pharmaceutical composition comprising [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) which is *obtained by, or is obtainable by*, a method as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

15 Another aspect of the present invention pertains to a method of preparing a pharmaceutical composition comprising admixing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

20 Another aspect of the present invention pertains to a method of preparing a pharmaceutical composition comprising admixing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) which is *obtained by, or is obtainable by*, a method as described herein, and a pharmaceutically acceptable carrier, diluent, or excipient.

Methods of Imaging etc.

25 Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging that employs [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

30 Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging that employs [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or is obtainable by*, a method as described herein.

35 Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging, that includes a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

40 Another aspect of the present invention pertains to a method of imaging, for example, a method of positron emission tomography (PET) imaging, that employs (i) an unlabelled

hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, for use in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or is obtainable by*, a method as described herein, for use in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or is obtainable by*, a method as described herein, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

Another aspect of the invention pertains to use of a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, as part of a method of imaging, for example, a method of positron emission tomography (PET).

Another aspect of the invention pertains to use of: (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.

In one embodiment, the method of imaging comprises the following steps:

(i) introducing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) into a subject;

(ii) imaging (e.g., a part of, the whole of) the subject.

In one embodiment, the step of (ii) imaging the subject is the step of (ii) determining the presence and/or location and/or amount of the [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) in (e.g., a part of, the whole of) the subject.

Methods of PET imaging are well known. See, for example, Czernin et al., 2002; Goh et al., 2003; Van Heertum et al., 2003; Fowler et al., 1999; Kennedy et al., 1997.

For example, in one embodiment, the method is a method of PET imaging comprising the steps of:

- (i) preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) using a method as described herein;
- (ii) introducing said compound into a subject; and
- (iii) PET imaging (e.g., a part of, the whole of) the subject.

Methods of Diagnosis or Prognosis etc.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that includes a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

Another aspect of the present invention pertains to a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, for use as a diagnostic or prognostic agent.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, for use as a diagnostic or prognostic agent.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, for use in a method of

diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

Another aspect of the present invention pertains to a method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body which includes a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.

Another aspect of the present invention pertains to a method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

In one embodiment, the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour (e.g., a cancer tumour characterised by the expression or over-expression of CYP1, e.g., CYP1B1).

In one embodiment, the diagnosis or prognosis is diagnosis or prognosis of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease; Pick's disease; Progressive Supranuclear Palsy (PSP); fronto-temporal dementia (FTD); parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD); cortico-basal degeneration (CBD)).

In one embodiment, the diagnosis or prognosis is diagnosis or prognosis of Alzheimer's disease.

In one embodiment, the method of diagnosis or prognosis comprises the following steps:

- (i) introducing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) into a subject;
- (ii) determining the presence and/or location and/or amount of [^{11}C]radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) in the subject;
- (iii) correlating the result of the determination made in (ii) with a disease condition of the subject.

Methods of Medical Treatment etc.

Another aspect of the present invention pertains to a method of treatment comprising administering an effective amount of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, to a patient in need of treatment.

Another aspect of the present invention pertains to a method of treatment of the human or animal body that comprises administering an effective amount of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, to a patient in need of treatment.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, for use in a method of treatment (e.g., of a disease condition) of the human or animal body by therapy.

Another aspect of the present invention pertains to [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, for use in a method of treatment (e.g., of a disease condition) of the human or animal body by therapy.

Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.

- 5 Another aspect of the present invention pertains to use of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or obtainable by*, a method described herein, in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.
- 10 Another aspect of the present invention pertains to use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.
- 15 Another aspect of the present invention pertains to a method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body which includes a method of preparing [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein.
- 20 Another aspect of the present invention pertains to a method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.
- 25 In one embodiment, the treatment is treatment of a cancer tumour (e.g., a cancer tumour characterised by the expression or over-expression of CYP1, e.g., CYP1B1).

In one embodiment, the treatment is treatment of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease; Pick's disease; Progressive Supranuclear Palsy (PSP); fronto-temporal dementia (FTD); parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD); cortico-basal degeneration (CBD)).

- 35 In one embodiment, the treatment is treatment of Alzheimer's disease.

Treatment

- 40 The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the

inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, regression of the condition, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis, prevention) is also included.

The term "therapeutically-effective amount," as used herein, pertains to that amount of an active compound, or a material, composition or dosage from comprising an active compound, which is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. Examples of treatments and therapies include, but are not limited to, chemotherapy (the administration of active agents, including, e.g., drugs, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

Routes of Administration

The [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), or pharmaceutical composition comprising it, may be administered to a subject/patient by any convenient route of administration, whether systemically/peripherally or topically (i.e., at the site of desired action).

Routes of administration include, but are not limited to, oral (e.g., by ingestion); buccal; sublingual; transdermal (including, e.g., by a patch, plaster, etc.); transmucosal (including, e.g., by a patch, plaster, etc.); intranasal (e.g., by nasal spray); ocular (e.g., by eyedrops); pulmonary (e.g., by inhalation or insufflation therapy using, e.g., via an aerosol, e.g., through the mouth or nose); rectal (e.g., by suppository or enema); vaginal (e.g., by pessary); parenteral, for example, by injection, including subcutaneous, intradermal, intramuscular, intravenous, intraarterial, intracardiac, intrathecal, intraspinal, intracapsular, subcapsular, intraorbital, intraperitoneal, intratracheal, subcuticular, intraarticular, subarachnoid, and intrasternal (including, e.g., intracatheter injection into the brain); by implant of a depot or reservoir, for example, subcutaneously or intramuscularly.

The Subject/Patient

The subject/patient may be an animal, mammal, a placental mammal, a marsupial (e.g., kangaroo, wombat), a monotreme (e.g., duckbilled platypus), a rodent (e.g., a guinea pig,

a hamster, a rat, a mouse), murine (e.g., a mouse), a lagomorph (e.g., a rabbit), avian (e.g., a bird), canine (e.g., a dog), feline (e.g., a cat), equine (e.g., a horse), porcine (e.g., a pig), ovine (e.g., a sheep), bovine (e.g., a cow), a primate, simian (e.g., a monkey or ape), a monkey (e.g., marmoset, baboon), an ape (e.g., gorilla, chimpanzee, orangutang, gibbon), or a human.

Furthermore, the subject/patient may be any of its forms of development, for example, a foetus.

In one preferred embodiment, the subject/patient is a human.

Formulations

While it is possible for the [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) to be used (e.g., administered) alone, it is often preferable to present it as a formulation.

One aspect of the present invention pertains to compositions comprising [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, and a pharmaceutically acceptable carrier, excipient, or diluent.

One aspect of the present invention pertains to compositions comprising [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, which is *obtained by, or is obtainable by*, a method as described herein, and a pharmaceutically acceptable carrier, excipient, or diluent.

In one embodiment, the composition is a pharmaceutical composition comprising [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, fillers, buffers, preservatives, anti-oxidants, lubricants, stabilisers, solubilisers, surfactants (e.g., wetting agents), masking agents, colouring agents, flavouring agents, and sweetening agents.

In one embodiment, the composition further comprises other active agents, for example, other therapeutic or prophylactic agents.

Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts. See, for example, Handbook of Pharmaceutical Additives, 2nd Edition (eds. M. Ash and I. Ash), 2001 (Synapse Information Resources, Inc., Endicott, New York, USA),

Remington's Pharmaceutical Sciences, 20th edition, pub. Lippincott, Williams & Wilkins, 2000; and Handbook of Pharmaceutical Excipients, 2nd edition, 1994.

Another aspect of the present invention pertains to methods of making a pharmaceutical composition comprising admixing [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), as described herein, together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, e.g., carriers, diluents, excipients, etc. If formulated as discrete units (e.g., tablets, etc.), each unit contains a predetermined amount (dosage) of the active compound.

The term "pharmaceutically acceptable" as used herein pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., human) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

The formulations may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active compound with carriers (e.g., liquid carriers, finely divided solid carrier, etc.), and then shaping the product, if necessary.

The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof.

Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the active ingredient is dissolved, suspended, or otherwise provided (e.g., in a liposome or other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. Typically, the concentration of the active ingredient in the liquid is from about 1 ng/mL to about 10 µg/mL, for example from about 10 ng/mL to about 1 µg/mL. The formulations may be presented in unit-dose or multi-dose sealed containers, for example,

ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

5

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), and compositions comprising
10 [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS), can vary from patient to patient. Determining the optimal dosage will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage level will depend on a variety of factors including, but not limited to, the activity of the
15 particular compound, the route of administration, the time of administration, the rate of excretion of the compound, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient. The amount of compound and route of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosage will be selected to achieve local
20 concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Administration can be effected in one dose, continuously or intermittently (e.g., in divided doses at appropriate intervals) throughout the course of treatment. Methods of
25 determining the most effective means and dosage of administration are well known to those of skill in the art and will vary with the formulation used for therapy, the purpose of the therapy, the target cell(s) being treated, and the subject being treated. Single or multiple administrations can be carried out with the dose level and pattern being selected by the treating physician, veterinarian, or clinician.

30

In general, a suitable dose of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) is in the range of about 100 ng to about 25 mg (more typically about 1 μg to about 10 mg) per kilogram body weight of the subject per day. Where the compound is a salt, an ester, an amide, a prodrug, or the like, the amount administered is calculated on the
35 basis of the parent compound and so the actual weight to be used is increased proportionately.

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

5

Chemical Synthesis

Chemicals and Solvents

10 All reagents were purchased from Sigma-Aldrich and used without further purification unless otherwise noted. All used solvents were purified and degassed according to standard procedures.

Analytical Methods

15

All analyses of the labelled compounds were performed with a GynkotheK HPLC system (P580 pump) and variable Wavelength UV/VIS detector (at 300 nm) coupled in series with a BIOSCAN NaI detector (B-FC-3200). The HPLC system was operated using a Phenomenex Luna C-18 column (150 x 3.0 mm, particle size: 5 µm). The eluent used
20 was HPLC grade acetonitrile and 0.1M ammonium formate solution (50:50). The eluent was filtered and degassed with helium before use. The flow rate was set at 1.2 mL/min.

Preparation of Silver Trifluoromethanesulfonate Column

25 A silver trifluoromethanesulfonate (silver triflate) column was prepared according to the method described by Jewett, 1992. Coarse silver triflate (1.0 g) and Graphpac-GC 80/100 (2.0 g, Alltech) was ground to a homogenous mixture. An empty stainless steel HPLC C-18 Luna column (250 x 3 mm) was loosely packed (10 cm length) with the mixture in the central region, and to restrain the packing material, both ends of the
30 column were then fitted with glass wool. Before the first reaction, the column was inserted into a tube furnace (Carbolite furnaces) and conditioned under argon gas flow for 30 minutes at 300°C.

[¹¹C]Carbon Dioxide Radiosynthesis

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[¹¹C]Carbon dioxide was prepared by proton bombardment of a gas mixture (98% N₂, 2% O₂) by the ¹⁴N(p,α)¹¹C nuclear reaction. The gas target was pressurised to 270 psi (1.9 MPa) and irradiated with 11 MeV protons produced by the CTI RDS-111 cyclotron at the John Mallard Scottish P.E.T. Centre in Aberdeen, Scotland. Irradiations of 10
40 minutes with a beam current of 27 µA were typically used.

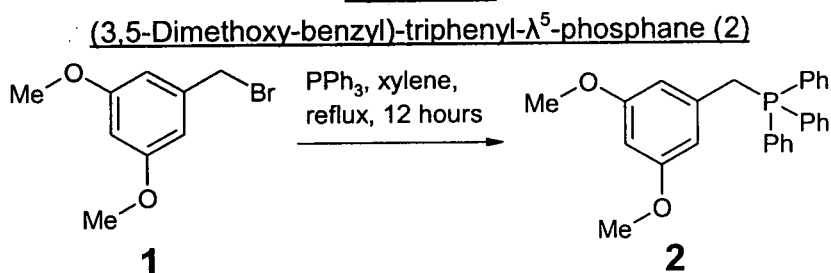
[¹¹C]Methyl Iodide Radiosynthesis

[¹¹C]Methyl iodide was prepared according to the traditional lithium aluminium hydride (LAH)/hydroiodic acid (HI) method (see, for example, Crouzel et al., 1987). At the "end of bombardment" (EOB), [¹¹C]carbon dioxide was transferred from the target in a stream of helium gas to the remote controlled automated [¹¹C]methyl iodide module, where it was passed into 200 µL of a cooled 0.1 M solution of lithium aluminium hydride (LAH) in tetrahydrofuran (THF). The [¹¹C]carbon dioxide reacted with LAH to produce the [¹¹C]methoxide anion. The first reaction vessel was then heated to 130°C to evaporate the solvent. After completing the THF evaporation, the contents of the reaction vessel were cooled to 0°C and 1 mL of 10% phosphoric acid was added to synthesise [¹¹C]methanol. [¹¹C]Methanol was then distilled into the second reaction vessel containing 600 µL of hydroiodic acid (HI). The second reaction vessel was heated to 135°C to produce on average 4.8 GBq of [¹¹C]methyl iodide. The average specific activity was 780 GBq/mmol.

[¹¹C] Methyl Trifluoromethanesulfonate Radiosynthesis

[¹¹C]Methyl trifluoromethanesulfonate ([¹¹C]methyl triflate) was prepared according to the method described by Jewett, 1992. In a stream of helium gas, the [¹¹C]methyl iodide was passed through the silver triflate graphpac column which was connected in series to the [¹¹C]methyl iodide module. The column was inserted into a tube furnace operated at 200°C, synthesising on average 2.0 GBq of [¹¹C]methyl triflate.

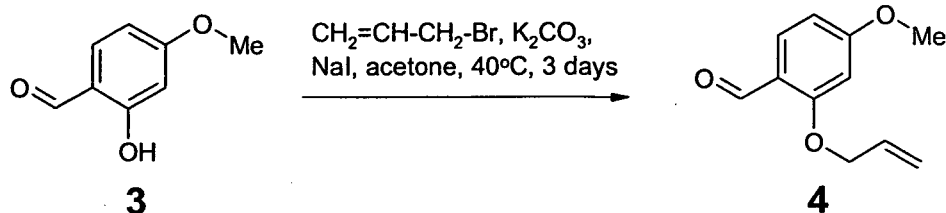
Synthesis 1



To a stirred solution of 1-bromomethyl-2,5-dimethoxybenzene (1) (5.0g; 21.64mmol) in 40 mL of xylene, a solution of triphenylphosphine (5.96 g, 22.72 mmol) in 10mL of xylene was added dropwise. The orange suspension was refluxed overnight. The flask was cooled down to room temperature and then placed in a freezer overnight. The precipitate was filtered, washed with cold xylene, and dried to give the title compound as a beige powdery solid (9.95 g; 20.13 mmol; 93%). C₂₇H₂₆O₂BrP (493.38 g/mol).

Synthesis 2

2-Allyloxy-4-methoxy-benzaldehyde (4)

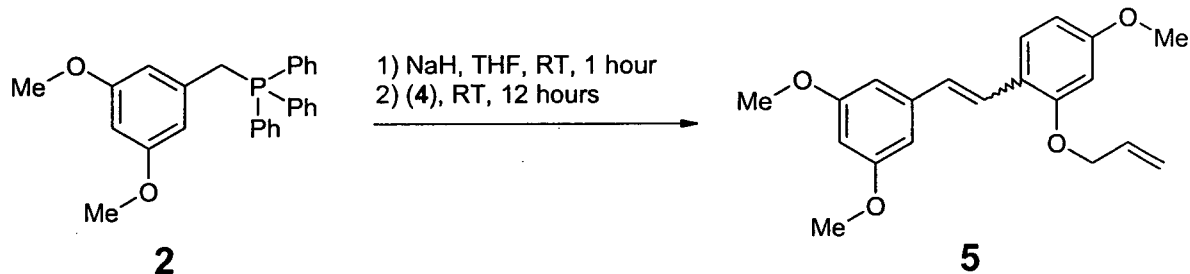


To a mixture of 2-hydroxy-4-methoxy-benzaldehyde (3.00 g, 19.73 mmol) and allylbromide (2.39 g, 19.73 mmol), potassium carbonate (K_2CO_3) (4.09 g, 29.60 mmol) and a catalytic amount of sodium iodide (3 mg, 19.7 μmol) was added. The reaction mixture was stirred at room temperature overnight. After 12 hours, the yellow mixture was heated to 40°C and stirred for 18 hours. 20 mL of acetone were added to the brown solution and the mixture was stirred for an additional 20 hours at 40°C . After concentration of the mixture, the residue was dissolved in dichloromethane and purified by column chromatography on silica gel (ethyl acetate / petrol ether, 1:7) to give the title compound (1.4 g; 7.30 mmol; 37%). $\text{C}_{11}\text{H}_{12}\text{O}_3$ (192.22 g/mol).

Synthesis 3

1,3-Dimethoxy-5-[(E)-2-(2-allyloxy-4-methoxy-phenyl)-vinyl]-benzene (5a)

1,3-Dimethoxy-5-[(Z)-2-(2-allyloxy-4-methoxy-phenyl)-vinyl]-benzene (5b)



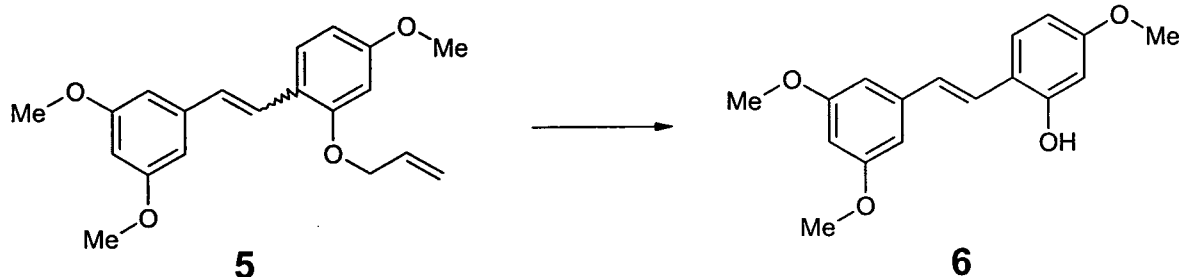
(3,5-Dimethoxy-benzyl)-triphenyl- λ^5 -phosphane (2) (3.60 g, 7.3 mmol) was added under nitrogen atmosphere to a cooled suspension of sodium hydride (0.25 g, 10.22 mmol) in 40 mL of anhydrous tetrahydrofuran (THF). The red suspension was stirred at 5°C for 30 minutes. A solution of 2-allyloxy-4-methoxy-benzaldehyde (4) (1.40 g, 7.3 mmol) in 10 mL of anhydrous THF was added dropwise. The reaction mixture was stirred at room temperature overnight. After concentration of the mixture, the residue was dissolved in 50 mL of diethyl ether and washed with water. The water phase was collected and extracted once with 50 mL of diethyl ether. The organic phases were combined, dried over sodium sulfate, and concentrated. Purification of the residual yellow oil using column chromatography on silica gel (ethyl acetate / petrol ether, 1:7) provided the (Z)-title compound (5b) (0.80 g; 2.45 mmol; 34%) as well as a mixture of the (E)-title compound (5a) and the (Z)-title compound (5b) (0.40 g; 1.23 mmol; 17%). $\text{C}_{20}\text{H}_{22}\text{O}_4$ (326.39 g/mol).

^1H NMR (400 MHz, CDCl_3) δ : 7.33 (d, $J = 8.4$ Hz, 1H), 7.17 (d, $J = 3.2$ Hz, 1H), 6.85 (d, $J = 16.4$ Hz, 1H), 6.58 (d, $J = 2$ Hz, 2H), 6.45-6.42 (dd, $J = 2.8$ Hz, $J = 8.8$ Hz, 1H), 6.30-6.29 (m, 2H), 3.74 (s, 2x- OCH_3 , 6H), 3.70 (s, - OCH_3 , 3H).

5

Synthesis 4

1,3-Dimethoxy-5-[(E)-2-(2-hydroxy-4-methoxy-phenyl)-vinyl]-benzene (6)



10 Sodium borohydride (NaBH_4) (0.09 g, 2.46 mmol) and a catalytic amount of tetrakis-(triphenylphosphin)-palladium ($\text{Ph}_3\text{Pd}(0)$) were added under nitrogen atmosphere to a solution of 1,3-dimethoxy-5-[(Z)-2-(2-allyloxy-4-methoxy-phenyl)-vinyl]-benzene (5b) (0.40 g, 1.23 mmol) in 50 mL of THF. The yellow solution was stirred at room temperature overnight. After evaporating the solvent, the residue was purified via column chromatography on silica gel (ethyl acetate / petrol ether, 1:2). The product isolated was dissolved in 50 mL of heptane. After adding a catalytic amount of iodine, the purple solution was refluxed for 2 hours. Concentration of the solution and subsequent purification via column chromatography on silica gel (ethyl acetate / petrolether, 1:2) provided pure title compound (6) as an orange viscous oil (0.11 g; 0.38 mmol, 31%).

15 $\text{C}_{20}\text{H}_{22}\text{O}_4$ (286.33g/mol).

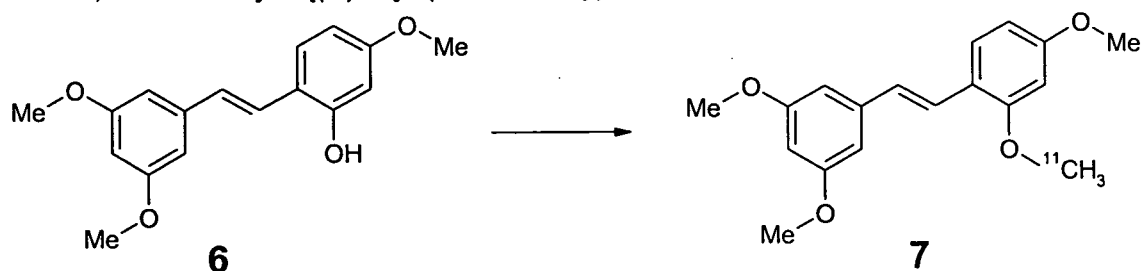
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^1H NMR (400 MHz, CDCl_3) δ : 7.33 (d, $J=8.4\text{Hz}$, 1H), 7.17 (d, $J= 3.2\text{Hz}$, 1H), 6.85 (d, $J= 16.4\text{Hz}$, 1H), 6.58 (d, $J=2\text{Hz}$, 2H), 6.45-6.42 (dd, $J = 2.8$ Hz $J = 8.8$ Hz, 1H), 6.30-6.29 (m, 2H), 3.74 (s, 2x- OCH_3 , 6H), 3.70 (s, - OCH_3 , 3H).

25

Synthesis 5

1,3-Dimethoxy-5-[(E)-2-[2-(^{11}C -methoxy)-4-methoxy-phenyl]-vinyl]-benzene (7)



1,3-Dimethoxy-5-[(E)-2-(2-hydroxy-4-methoxy-phenyl)-vinyl]-benzene (6) (1 mg, 3.49 μmol) was dissolved in 200 μL of anhydrous acetonitrile in a dry pyrex test tube

30

under argon atmosphere and treated with K_2CO_3 (10 mg, 72.36 μ mol). The test tube was sealed with a rubber stopper and heated at 37°C for 2 hours. The methylating agent [^{11}C]methyl triflate was bubbled through the test tube via a spinal needle (18 GA, 90 mm) for 2 minutes. After the end of [^{11}C]methyl triflate collection, the reaction mixture was transferred on to a C-18 Sep-Pak Plus cartridge (Waters) which was subsequently washed with 15 mL of sterile water at room temperature. Then the cartridge was rinsed with 1.5 mL of ethanol to provide the title compound (7) as a solution in ethanol.

20 μ L of the mixture flushed off the C-18 cartridge by the ethanol was injected into a C-18 Luna 5 μ m (250 mm x 3 mm) Phenomenex column and eluted with 50:50 mixture of acetonitrile and 0.1 M ammonium formate at a flow rate of 1.4 mL at 35°C. Radioactive components were detected using an in-line radiation detector. The identity of the radiolabelled product (7) was confirmed via co-injection with a commercial sample of 1,3-dimethoxy-5-[(E)-2-(2,4-dimethoxy-phenyl)-vinyl]-benzene. The retention was compared with the retention time of a 20 μ L sample of commercially available form of 1,3-dimethoxy-5-[(E)-2-(2,4-dimethoxy-phenyl)-vinyl]-benzene (1 mg/mL) (Cayman Chemicals, Ann Arbor USA) detected using UV (Gynkotec model UVD 340s) at 300 nm. The retention time in the UV-chromatogram was nearly identical to the retention time of the radiolabelled product (7) in the radioactivity-chromatogram. See Figure 1.

In all studies, the radiolabelled product (7) was obtained with a radiochemical purity greater than 95% in an averaged 20% radiochemical yield based on [^{11}C]methyl iodide. The average specific activity was 3 GBq/ μ mol.

Figure 1 shows (top) the UV chromatogram (UV absorbance versus time) recorded for a solution of the radiolabelled compound 1,3-dimethoxy-5-[(E)-2-[2-(^{11}C -methoxy)-4-methoxy-phenyl]-vinyl]-benzene (7) showing a retention time of 21.4 minutes; and (bottom) the radioactivity chromatogram (radioactivity versus time) recorded for the same solution (radiochemical purity 91%), showing a retention time of 21 minutes. (The peaks at 18.7 and 29.9 minutes are unidentified.)

The radiolabelled compound was obtained with a radiochemical purity of greater than 95% in an averaged yield of 20% based on [^{11}C]methyl iodide. The average specific activity was 3 GBq/ μ mol. The total synthesis time from EOB was about 30 minutes.

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described embodiments should be regarded as illustrative rather than restrictive, and it should be appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention as defined by the appended claims.

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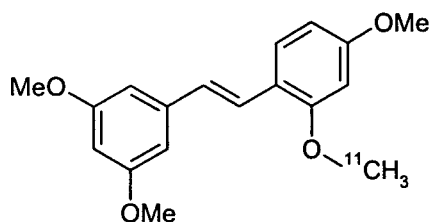
A number of references are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

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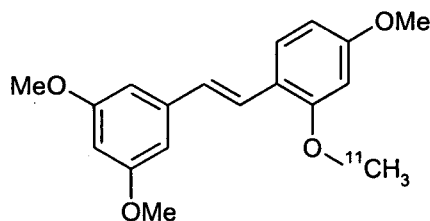
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- 25

CLAIMS

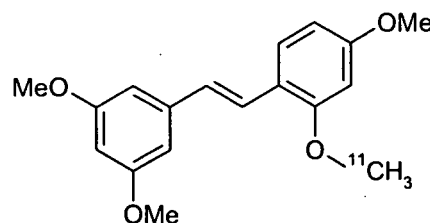
1. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound selected from [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) and pharmaceutically acceptable salts, solvates, and hydrates thereof.
2. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound selected from compounds of the following formula and pharmaceutically acceptable salts, solvates, and hydrates thereof:



3. A compound according to claim 2, wherein the compound is:

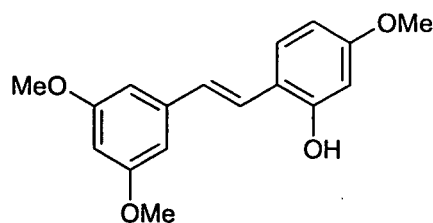


4. A method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound comprising the step of reacting an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) that has a pendant hydroxyl group with [^{11}C]methyl triflate or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$) so as to convert said pendant hydroxyl group into a pendant [^{11}C]methoxy group.
5. A method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound of the following formula:



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said method comprising the step of reacting a compound of the following formula:



with [^{11}C]methyl triflate or [^{11}C]methyl iodide ($^{11}\text{CH}_3\text{I}$) to give said [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound.

6. A method according to claim 4 or 5, wherein said step of reacting is reacting with [^{11}C]methyl triflate.
7. A method according to claim 4 or 5, wherein said step of reacting is reacting with [^{11}C]methyl iodide.
8. A method according to any one of claims 4 to 7, wherein said reaction is performed in the presence of a Bronsted base.
9. A method according to any one of claims 4 to 7, wherein said reaction is performed in the presence of an alkali metal carbonate or bicarbonate.
10. A method according to any one of claims 4 to 7, wherein said reaction is performed in the presence of potassium carbonate (K_2CO_3).
11. A method according to any one of claims 4 to 10, wherein said reaction is carried out in aqueous media.
12. A method according to any one of claims 4 to 11, wherein said reaction is carried out by introducing said [^{11}C]methyl triflate or [^{11}C]methyl iodide into an aqueous solution or suspension of unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) to form a reaction mixture.
13. A method according to claim 12, wherein said aqueous solution or suspension further comprises a Bronsted base.
14. A method according to claim 12, wherein said aqueous solution or suspension further comprises an alkali metal carbonate or bicarbonate.
15. A method according to claim 12, wherein said aqueous solution or suspension further comprises potassium carbonate (K_2CO_3).

16. A method according to any one of claims 12 to 15, wherein said reaction mixture is mixed for a mixing time of 1-30 minutes.
- 5 17. A method according to any one of claims 12 to 15, wherein said reaction mixture is mixed for a mixing time of 1-10 minutes.
18. A method according to any one of claims 12 to 17, wherein said reaction is carried out at 20°C-25°C.
- 10 19. A method according to any one of claims 12 to 18, wherein said reaction is carried out under an inert atmosphere.
20. A method according to any one of claims 12 to 18, wherein said reaction is carried out under argon.
- 15 21. A method according to any one of claims 4 to 20, further comprising the subsequent step of purifying said [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound.
- 20 22. A method according to any one of claims 4 to 20, further comprising the subsequent step of purifying said [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound using ion exchange methods.
- 25 23. A method according to any one of claims 4 to 20, further comprising the subsequent step of purifying said [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound using cation exchange methods.
24. A method according to any one of claims 4 to 23, wherein the reaction and optional purification is performed in less than 60 minutes.
- 30 25. A method according to any one of claims 4 to 23, wherein the reaction and optional purification is performed in less than 45 minutes.
26. A method according to any one of claims 4 to 23, wherein the reaction and optional purification is performed in less than 40 minutes.
- 35 27. A method according to any one of claims 4 to 26, which provides a radiochemical purity greater than 90%.
- 40 28. A method according to any one of claims 4 to 27, which provides a radiochemical yield of at least 2%.

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29. A method according to any one of claims 4 to 28, which provides a specific average activity of at least 0.5 GBq/μmol.

5 30. A method according to any one of claims 4 to 29, which is partially or fully automated.

* * *

10 31. A [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound which is *obtained* by a method as defined in any one of claims 4 to 30.

32. A [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound which is *obtainable* by a method as defined in any one of claims 4 to 30.

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* * *

33. A pharmaceutical composition comprising a [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 and a pharmaceutically acceptable carrier, diluent, or excipient.

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34. A method of preparing a pharmaceutical composition comprising admixing a [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 and a pharmaceutically acceptable carrier, diluent, or excipient.

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* * *

35. A method of imaging, for example, a method of positron emission tomography (PET) imaging that employs a [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32.

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36. A method of imaging, for example, a method of positron emission tomography (PET) imaging, that includes a method of preparing a [¹¹C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 4 to 30.

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37. A method of imaging, for example, a method of positron emission tomography (PET) imaging, that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) CF₃SO₂O¹¹CH₃ or ¹¹CH₃I.

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38. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 for use in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.
39. Use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.
40. Use of a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 4 to 30 as part of a method of imaging, for example, a method of positron emission tomography (PET).
41. Use of: (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$, in a method of imaging, for example, in a method of positron emission tomography (PET) imaging.
42. A method, compound, or use according to any one of claims 35 to 41, wherein said method of imaging comprises the following steps:
(i) introducing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound into a subject;
(ii) imaging (e.g., a part of, the whole of) the subject.
43. A method, compound, or use according to claim 42, wherein the step of (ii) imaging the subject is the step of (ii) determining the presence and/or location and/or amount of [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound in (e.g., a part of, the whole of) the subject.
- * * *
44. A method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32.
45. A method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 4 to 30.

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46. A method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.

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* * *

47. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 for use as a diagnostic or prognostic agent.

10

48. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

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* * *

49. Use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

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50. Use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body.

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51. A method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body which includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 4 to 30.

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52. A method for the manufacture of a medicament (e.g., a diagnostic or prognostic reagent) for use in a method of diagnosis or prognosis (e.g., of a disease condition) practiced on the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.
53. A method, compound, or use according to any one of claims 44 to 52, wherein the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour.
54. A method, compound, or use according to any one of claims 44 to 52, wherein the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour characterised by the expression or over-expression of CYP1.
55. A method, compound, or use according to any one of claims 44 to 52, wherein the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour characterised by the expression or over-expression of CYP1B1.
56. A method, compound, or use according to any one of claims 44 to 52, wherein the diagnosis or prognosis is diagnosis or prognosis of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease; Pick's disease; Progressive Supranuclear Palsy (PSP); fronto-temporal dementia (FTD); parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD); cortico-basal degeneration (CBD)).
57. A method, compound, or use according to any one of claims 44 to 52, wherein the diagnosis or prognosis is diagnosis or prognosis of Alzheimer's disease.
58. A method, compound, or use according to any one of claims 44 to 57, wherein the method of diagnosis or prognosis comprises the following steps:
(i) introducing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound into a subject;
(ii) determining the presence and/or location and/or amount of said [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound in the subject;
(iii) correlating the result of the determination made in (ii) with a disease condition of the subject.

* * *

59. A method of treatment comprising administering an effective amount of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 to a patient in need of treatment.
- 5 60. A [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 for use in a method of treatment (e.g., of a disease condition) of the human or animal body by therapy.
- 10 61. Use of a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 1 to 3 and 31 to 32 in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.
- 15 62. Use of (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$ in the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body.
- 20 63. A method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body which includes a method of preparing a [^{11}C]methoxy-radiolabelled 2,3',4,5'-tetramethoxystilbene (TMS) compound according to any one of claims 4 to 30.
- 25 64. A method for the manufacture of a medicament for the treatment (e.g., of a disease condition) of the human or animal body that employs (i) an unlabelled hydroxy precursor of 2,3',4,5'-tetramethoxystilbene (TMS) and (ii) $\text{CF}_3\text{SO}_2\text{O}^{11}\text{CH}_3$ or $^{11}\text{CH}_3\text{I}$.
- 30 65. A method, compound, or use according to any one of claims 59 to 64, wherein the treatment is treatment of a cancer tumour.
- 35 66. A method, compound, or use according to any one of claims 59 to 64, wherein the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour characterised by the expression or over-expression of CYP1.
67. A method, compound, or use according to any one of claims 59 to 64, wherein the diagnosis or prognosis is diagnosis or prognosis of a cancer tumour characterised by the expression or over-expression of CYP1B1.

- 5 68. A method, compound, or use according to any one of claims 59 to 64, wherein the diagnosis or prognosis is diagnosis or prognosis of a disorder associated with beta amyloid plaques (e.g., Alzheimer's disease; Pick's disease; Progressive Supranuclear Palsy (PSP); fronto-temporal dementia (FTD); parkinsonism linked to chromosome 17 (FTDP-17); disinhibition-dementia-parkinsonism-amyotrophy complex (DDPAC); pallido-ponto-nigral degeneration (PPND); Guam-ALS syndrome; pallido-nigro-luysian degeneration (PNLD); cortico-basal degeneration (CBD)).
- 10 69. A method, compound, or use according to any one of claims 59 to 64, wherein the diagnosis or prognosis is diagnosis or prognosis of Alzheimer's disease.

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FIGURE 1

